PK/PD to fight resistance

- Eradicate
  - Abnormal bacteria
  - Mutations
  - Efflux pumps
- Mutation-Preventing Concentration
- Breakpoint values for T > MIC
- and in practice …

With the support of *Wallonie-Bruxelles-International*

Mutant selection : role of antibiotics ...

gene

enzyme / nucleoproteine

fonction

Poorly active antibiotics...

The worse you can do is to not kill bacteria !!!

therefore, eradicate ...

JOURNAL OF CLINICAL MICROBIOLOGY, Aug. 1982, p. 382–386
0095-1137/82/080382-05$02.00/0

Vol. 16, No. 2

Unkilled bacteria look abnormal … this has been known for a long time

NOTES

Abnormal Morphology of Bacteria in the Sputa of Patients Treated with Antibiotics

VICTOR LORIAN,* ALEXANDRA WALUSCHKA, AND YEHUM KIM

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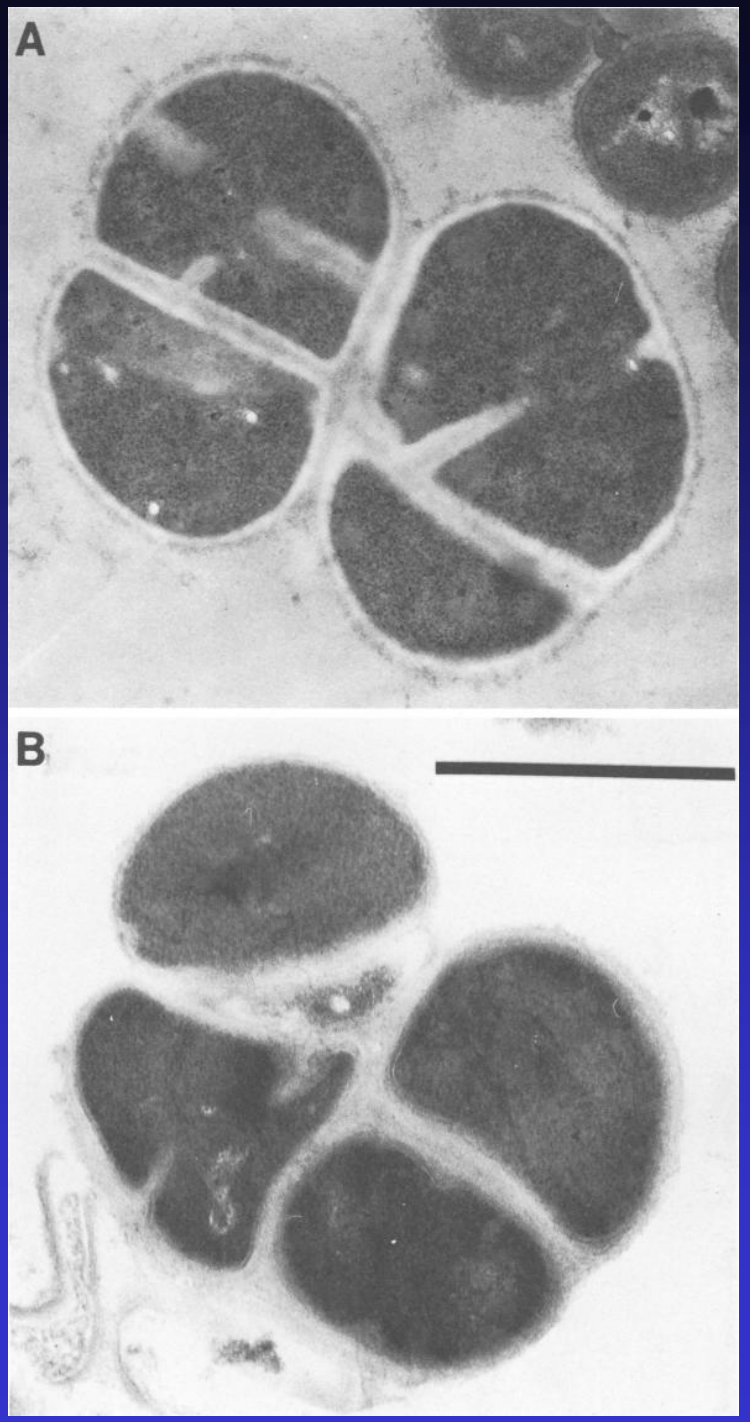
Received 13 January 1982/Accepted 2 April 1982

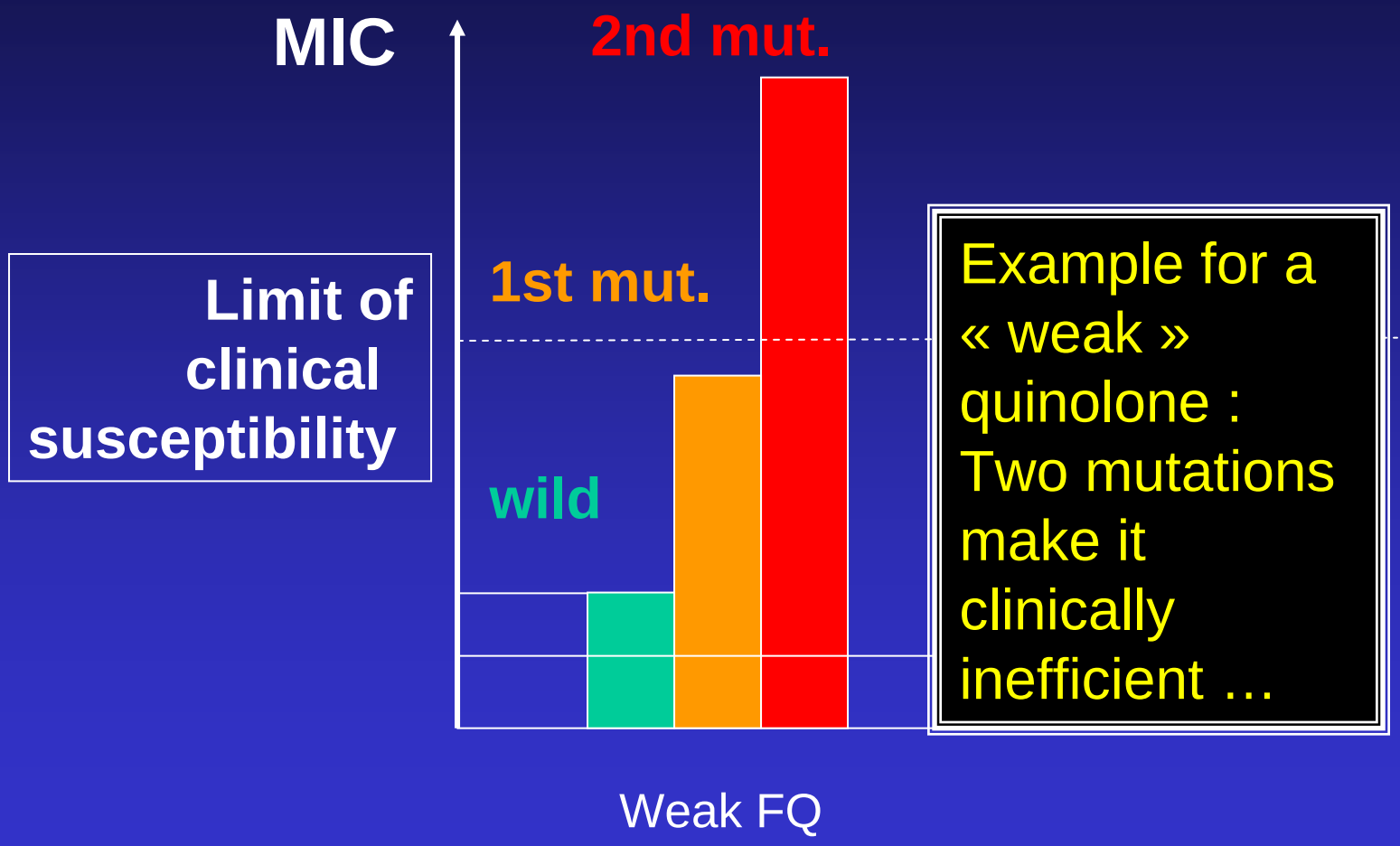
Filaments of *Klebsiella pneumoniae* were observed by Gram stain in the sputum of a patient with a respiratory infection who was treated with half the usual dose of cefazolin. Identical filaments were observed in vitro when this strain was incubated with subminimum inhibitory concentrations of cefazolin. Large gram-positive cocci containing multiple cross walls were observed by electron microscopy in the sputum of a patient with a respiratory infection who was treated with ampicillin and gentamicin. Antibiotic administration was suspended the night before the sputum was obtained. The ultrastructure of these cocci was very similar to the ultrastructure of *Staphylococcus aureus* incubated with subminimum inhibitory concentrations of cephaloridine or oxacillin. It was suspected that the low dose of cefazolin and the intermittent therapy with ampicillin resulted in a subminimum inhibitory concentration of antibiotic in the respiratory tract which induced the abnormal morphology of the bacteria observed in the sputum of both patients. The presence of abnormal forms of bacteria in the specimen of a patient, rather than in the culture of a specimen, has clinical significance.

Pictures of abnormal bacteria upon exposure to subinhibitory concentrations …

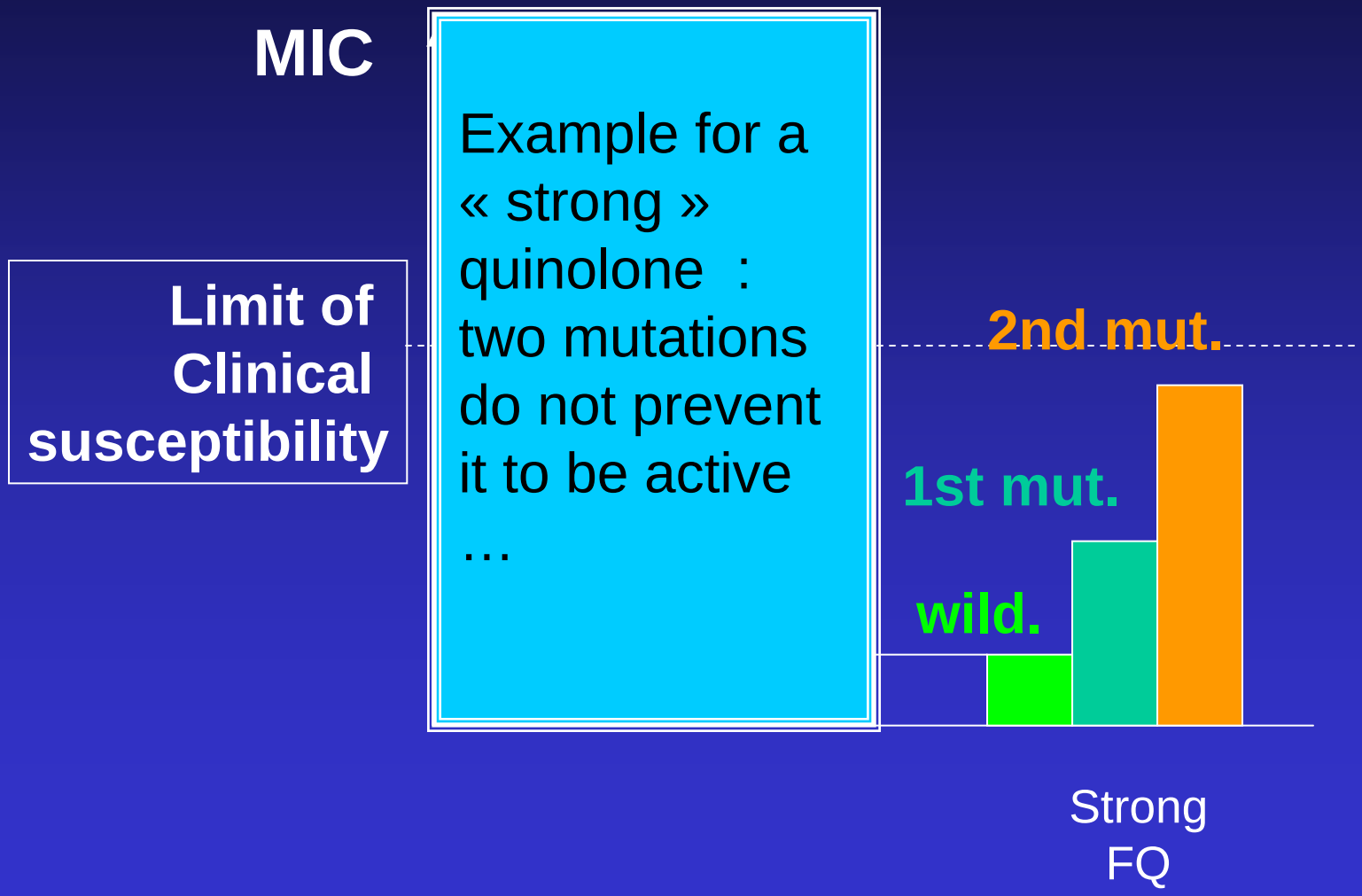


Lorian et al., J. Clin. Microbio. 16:382-386,1982

Less potent antibiotics are more prone to loose their activity against mutated targets …

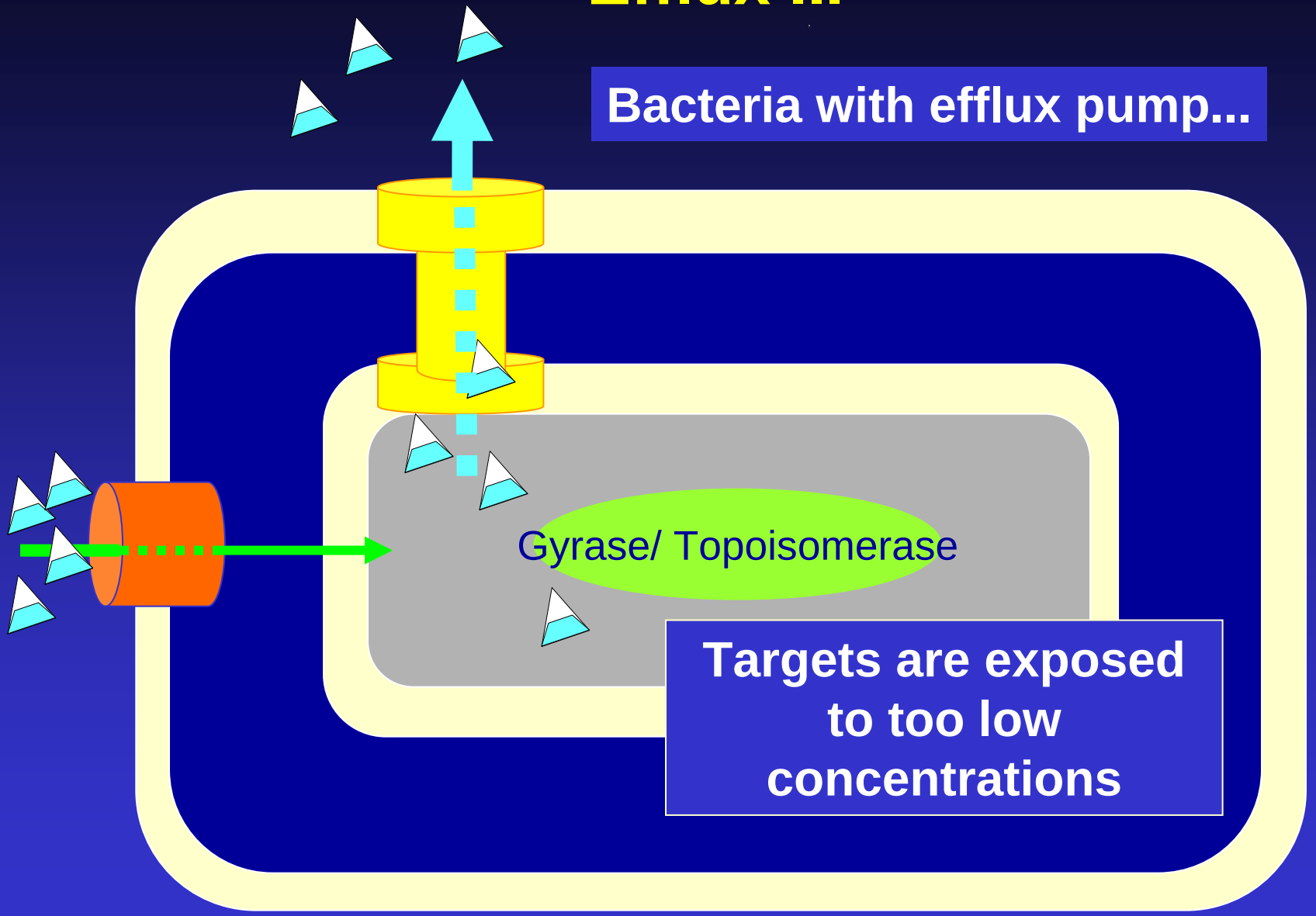


In contrast, more potent antibiotics remain active even on first-step mutants…

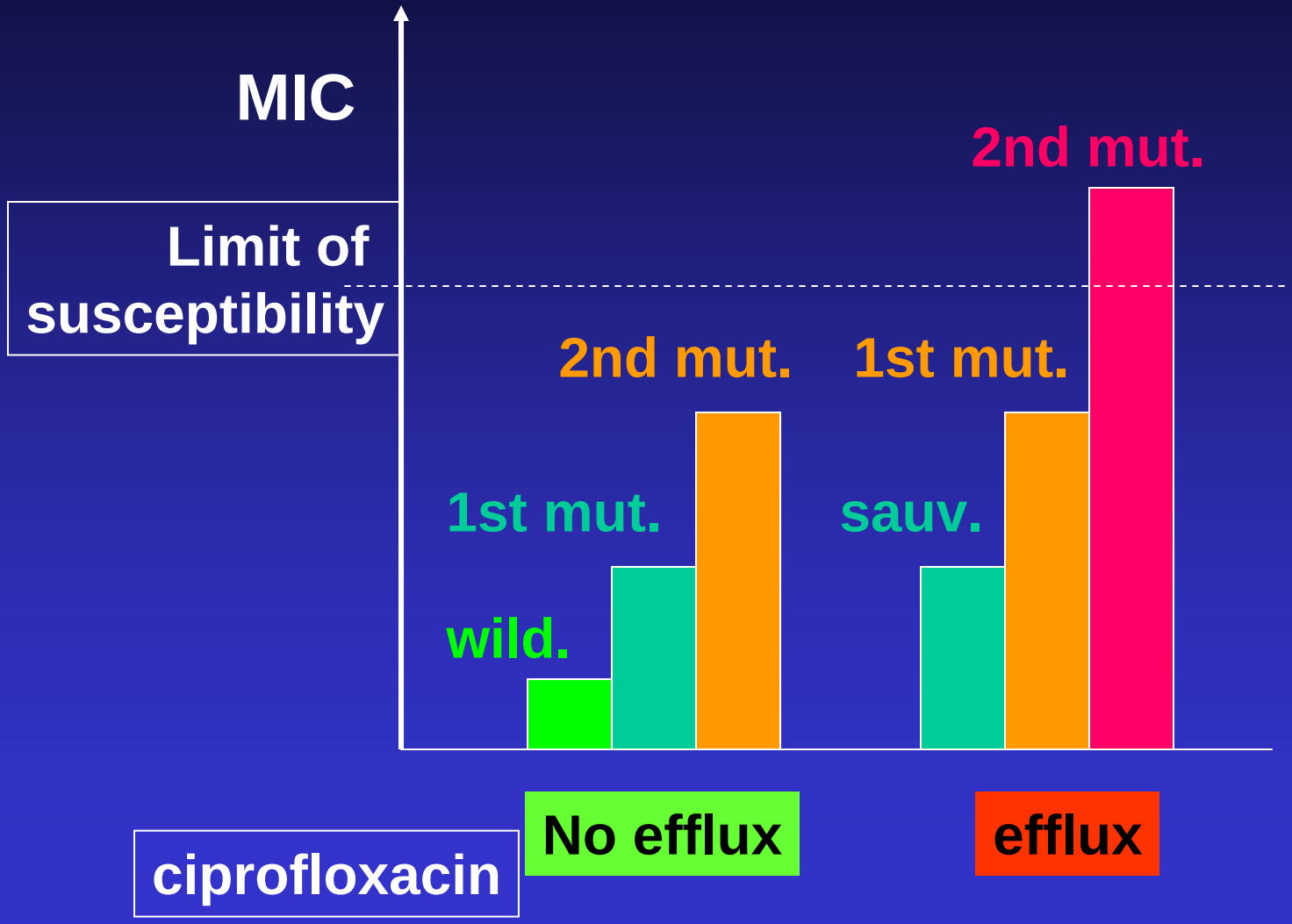


Efflux ...

Bacteria with efflux pump...



Efflux and mutations cooperate to surpass the susceptibility limit ...

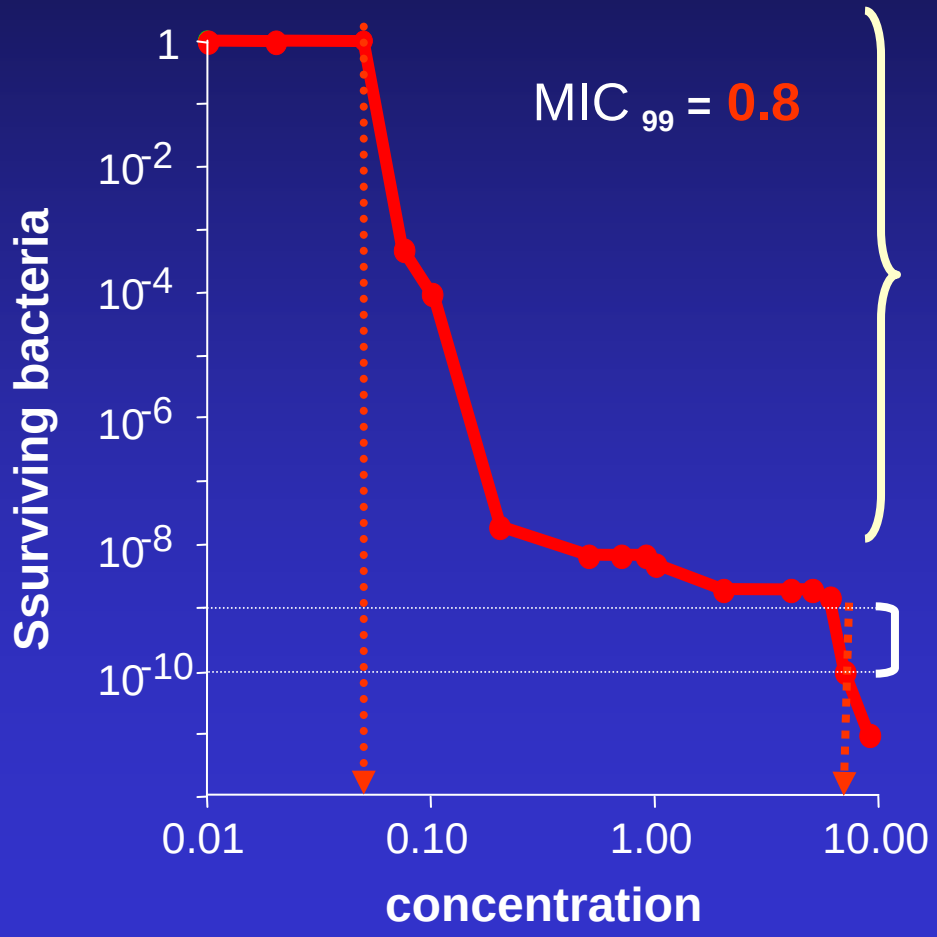


4 reasons to eradicate …

- Killed bacteria do not mutate anymore …
  (simple application of Darwin's concepts…)
- If they are killed, they cannot contaminate their neighbors …
  (basic principle for epidemiology actions …)
- After all, if Pasteur is right (and he is…), don't we need to eliminate the pathogen to cure ?
  (physiopathological basis of infectious diseases…)
- Don't you wish that you patient recovers more quickly and defenitely ?
  (a satisfied patient will be faithfully)

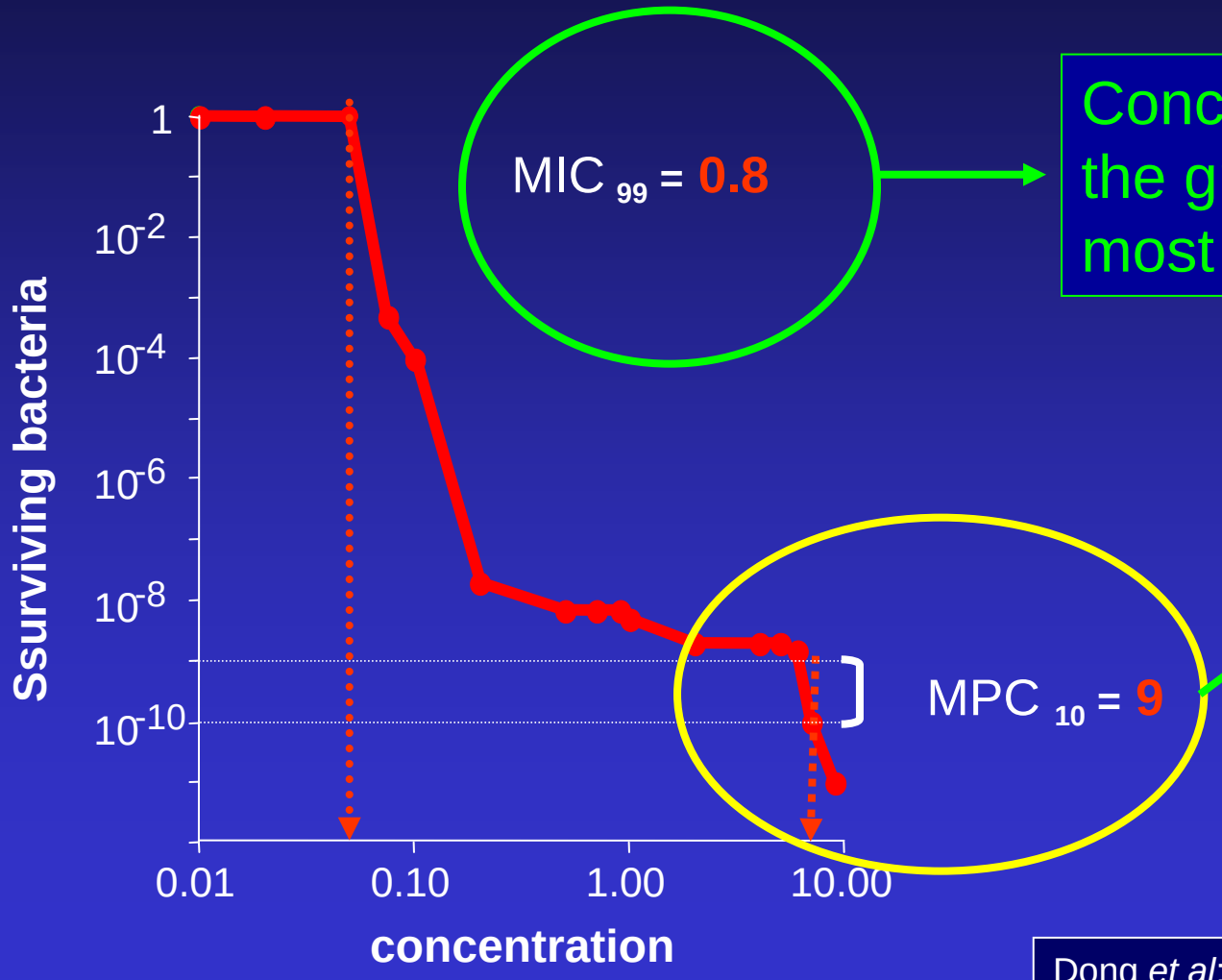
Mutation-Preventing Concentration (MPC)...

Example: bactericidal activity of FQs vs *Mycobacterium bovis*



Dong *et al*; AAC 43:1756-1758

Mutation-Preventing Concentration (MPC)...

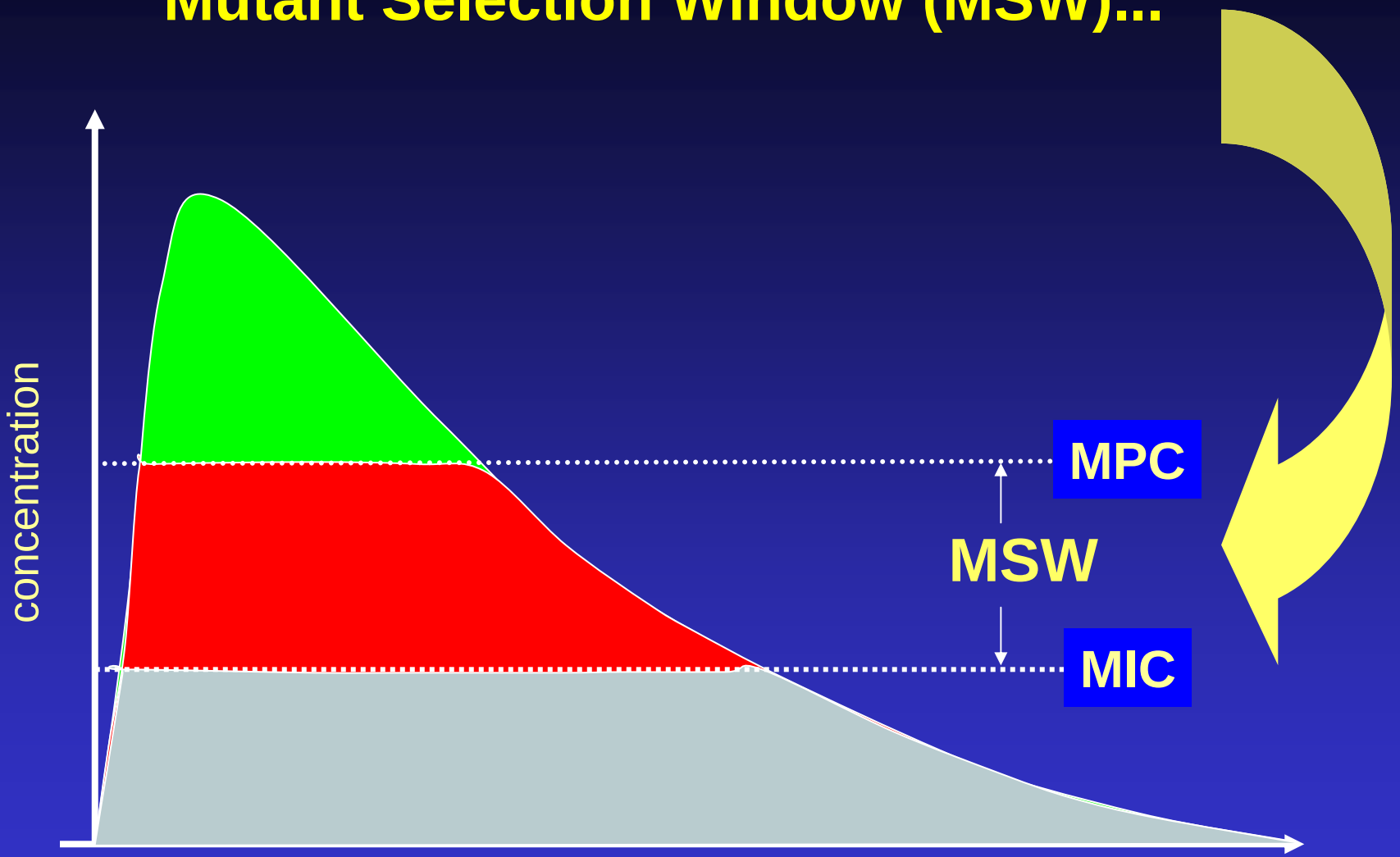


Concentration inhibiting the growth of most organisms

concentration required to prevent thea selection of first-step mutants

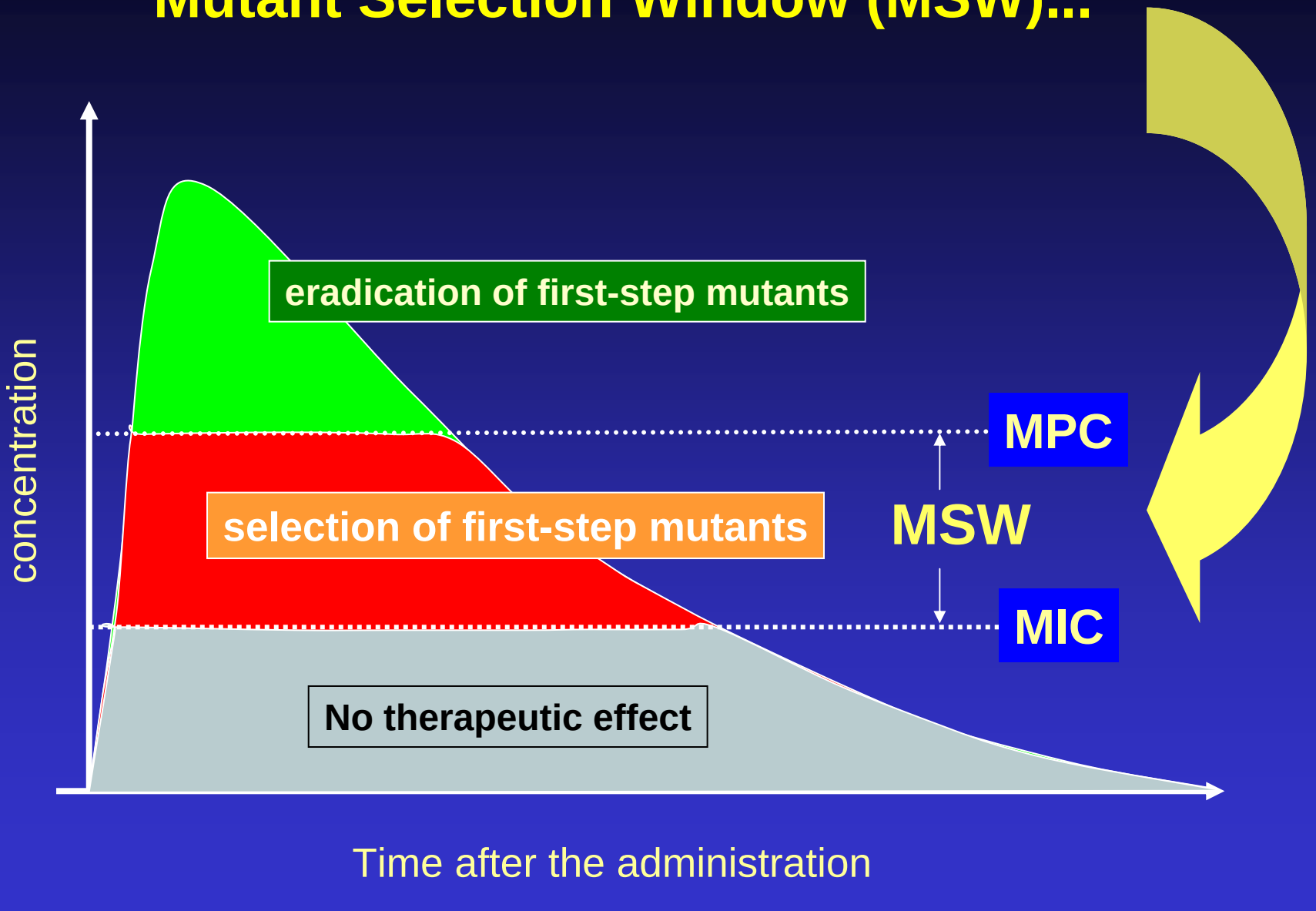
Dong *et al*; AAC 43:1756-1758

Mutant Selection Window (MSW)...



concept adapted from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

Mutant Selection Window (MSW)...

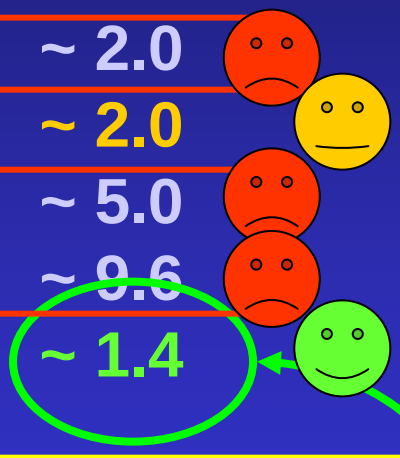


concept adapted from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

Mutant Selection Window (MSW)...

PK/PD and MPC: stay above the MPC to avoid mutant selection

Drug	Dosage (unitary)	C_{max} (mg/L)	observed MPC (mg/L)
norfloxacin	400	1.2 *	~ 2.0
ciprofloxacin	500	2.4 *	~ 2.0
ofloxacin	200	1.5-3 *, +	~ 5.0
levofloxacin	500	5-6 *, +	~ 9.6
moxifloxacin	400	4.5 *	~ 1.4



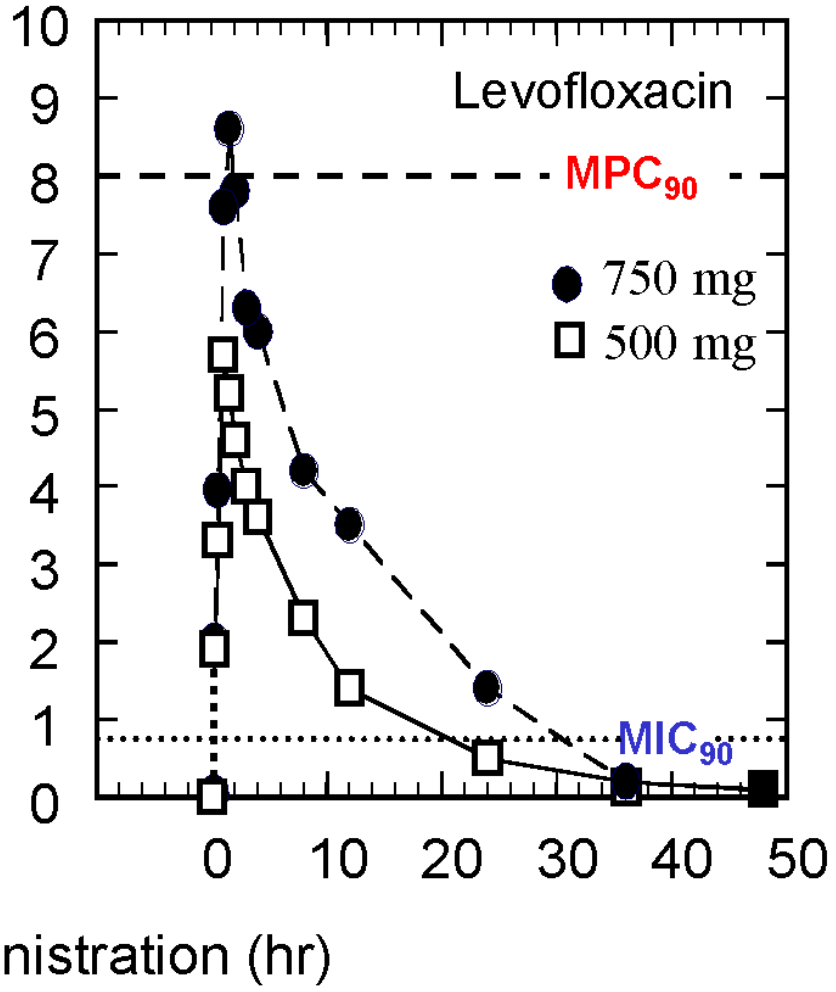
* Data from registration files
\# literature data;
\+ first dose and equilibrium

Due to the presence of C8-methoxy

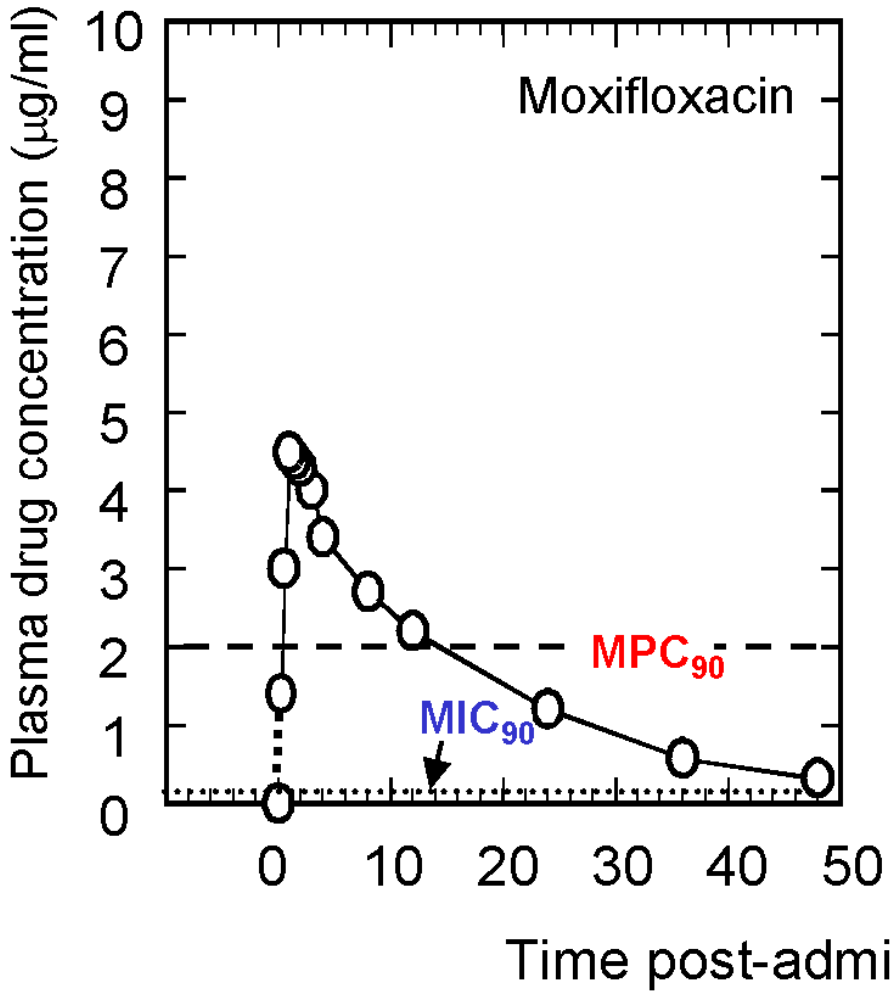
MPC and levofloxacin in practice...

for levofloxacin,
serum concentrations remain
> MIC during 20 h
BUT are always < MPC
Of pneumococci

High risk for selection of resistance !



MPC and moxifloxacin in practice ...



In contrast, for moxifloxacin, serum concentations remain above the MPC of pneumococci during at least 14 h

Lower risk for selection of resistance

Exercise with fluoroquinolones...

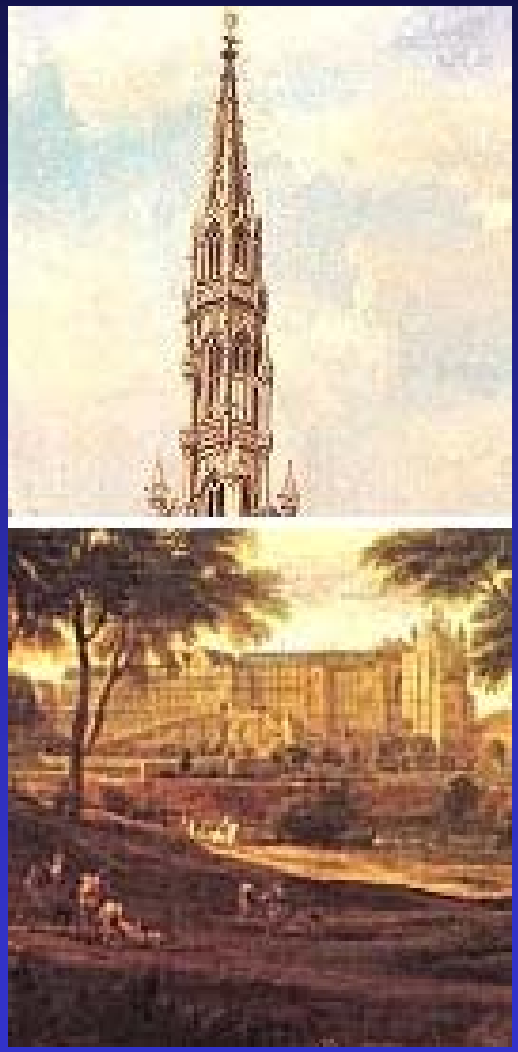
Prevention of resistance and efficacy:

- peak / MIC > 12

  and/or > MPC

- AUC / MIC > 100

  (non fully immunocompetent patients)



AUC_{24h} / MIC = 125 **AND** Peak / MIC > 10 as parameters defining the limit of susceptibility to FQ

FQ	Dose (mg/24h)	PK/PD breakpoint (mg/L) based on **AUC/MIC ***	PK/PD breakpoint (mg/L) based on **peak / CMI ‡**
norfloxacin	800	**0.1**	**0.2**
ciprofloxacin	1200	**0.5**	**0.25**
ofloxacine	200	**0.1-0.2**	**0.15 - 0.2**
levofloxacin	500	**0.5**	**0.4 - 0.5**
moxifloxacin	400	**0.5**	**0.5**

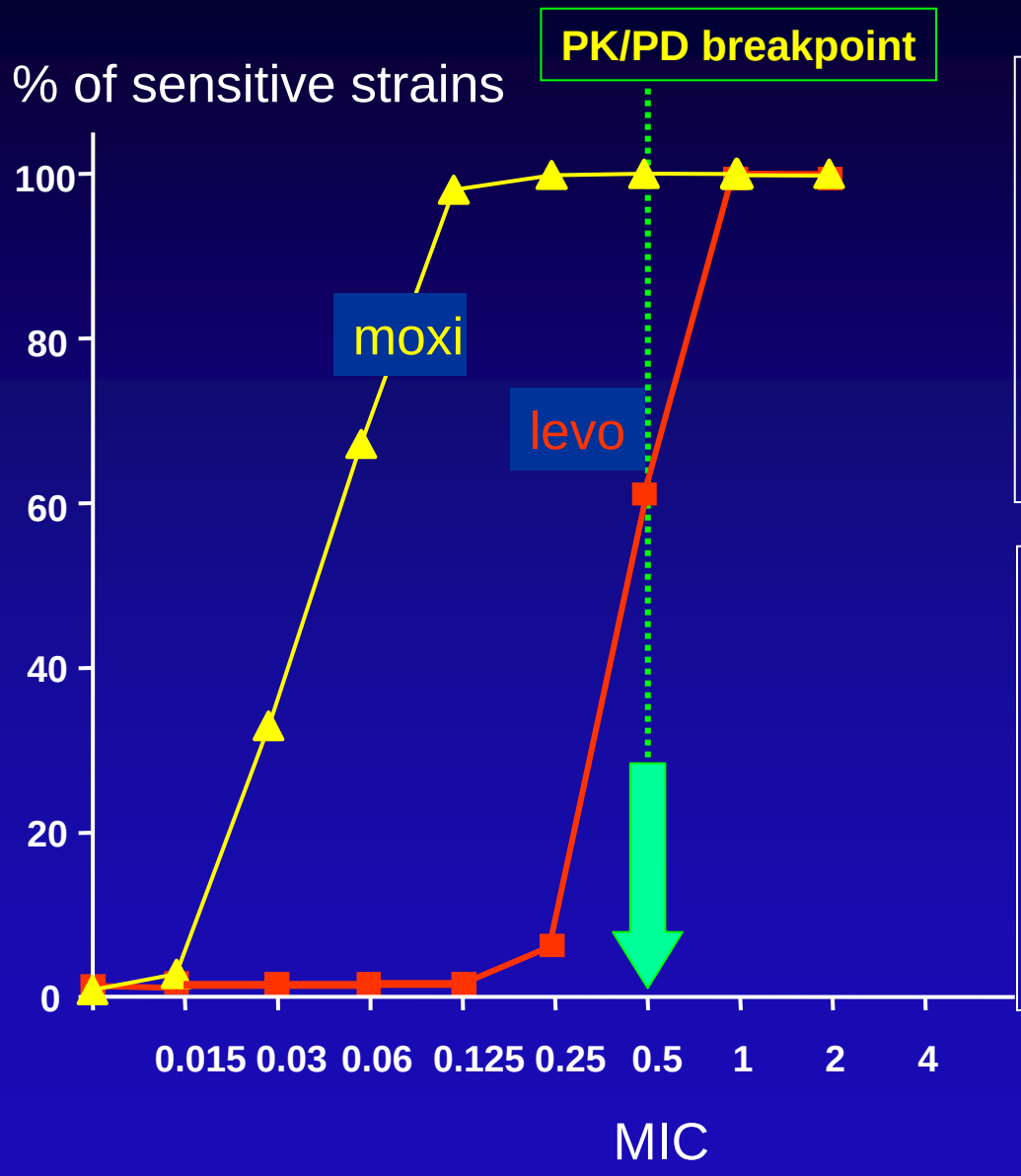
* AUC for 24 h doses
‡ C_{max} for recommended unitary doses

AUC_{24h} / MIC = 125 **AND** Peak / MIC > 10 as parameters defining the limit of susceptibility to FQ

FQ	Dose (mg/24h)	PK/PD breakpoint (mg/L) based on **AUC/MIC ***	PK/PD breakpoint (mg/L) based on **peak / CMI ‡**	**CLSI Bkpt** (mg/L)
norfloxacin	800	**0.1**	**0.2**	**4**
ciprofloxacin	1200	**0.5**	**0.25**	**1**
ofloxacine	200	**0.1-0.2**	**0.15 - 0.2**	**2**
levofloxacin	500	**0.5**	**0.4 - 0.5**	**2**
moxifloxacin	400	**0.5**	**0.5**	**2**

* AUC for 24 h doses
‡ C_{max} for recommended unitary doses

Application to pneumococci from Belgium



Levofloxacin 500 mg 1X /day

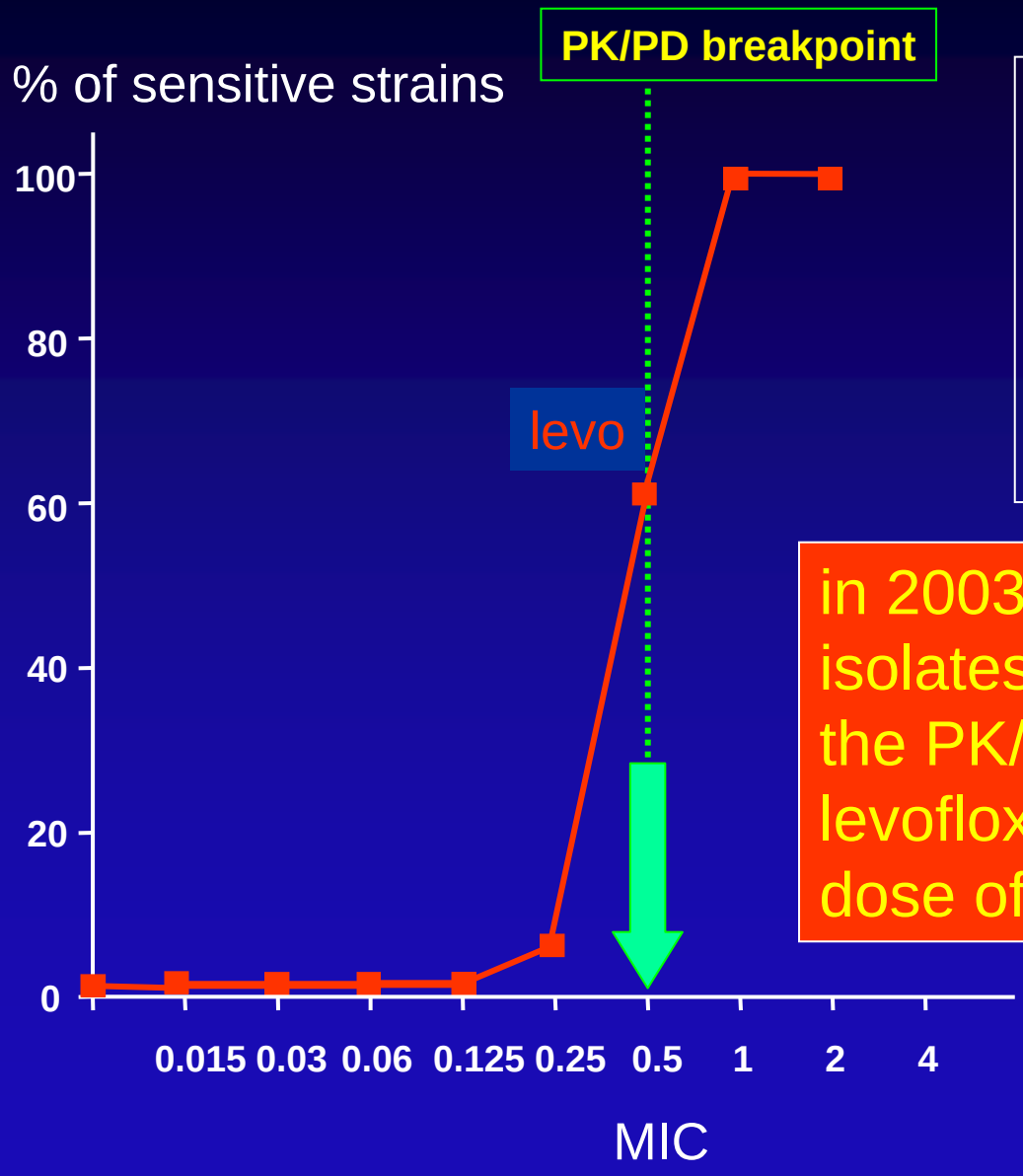
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- MIC_{max} < 0.5

Moxifloxacin 400 mg 1X/day

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
- MIC_{max} < 0.5

MIC data: J. Verhaegen et al., 2003

Application to pneumococci from Belgium



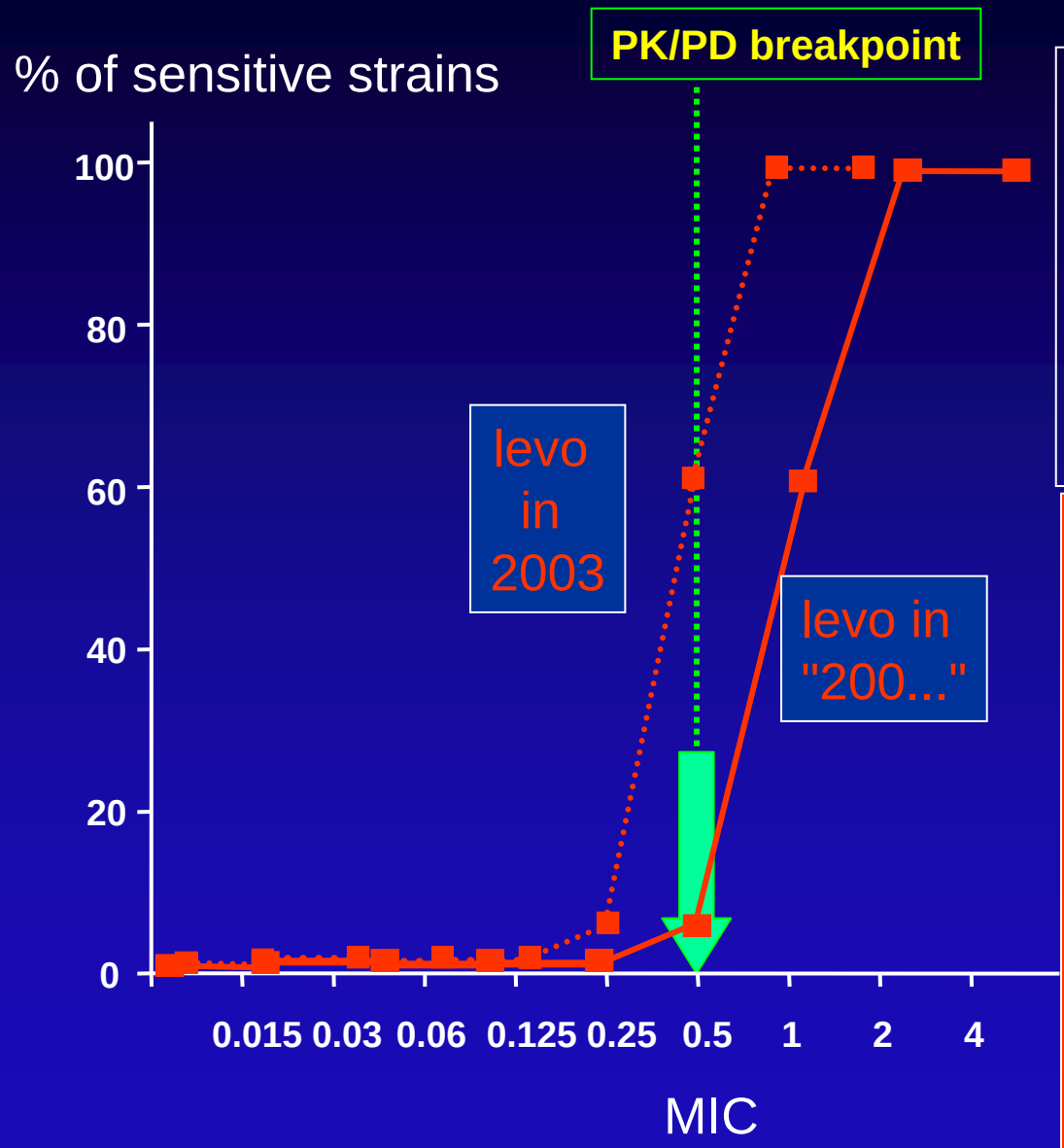
Levofloxacin 500 mg 1X /day

- AUC [(mg/l)xh] 47
- peak [mg/l] 5
  - MIC_{max} < 0.5

in 2003, about 40 % of Belgian isolates had MIC higher than the PK/PD breakpoint if levofloxacin is used at a daily dose of 500 mg

MIC data: J. Verhaegen et al., 2003

Why do we fear a rapid emergence of resistance to levofloxacin in pneumococci in Belgium ?

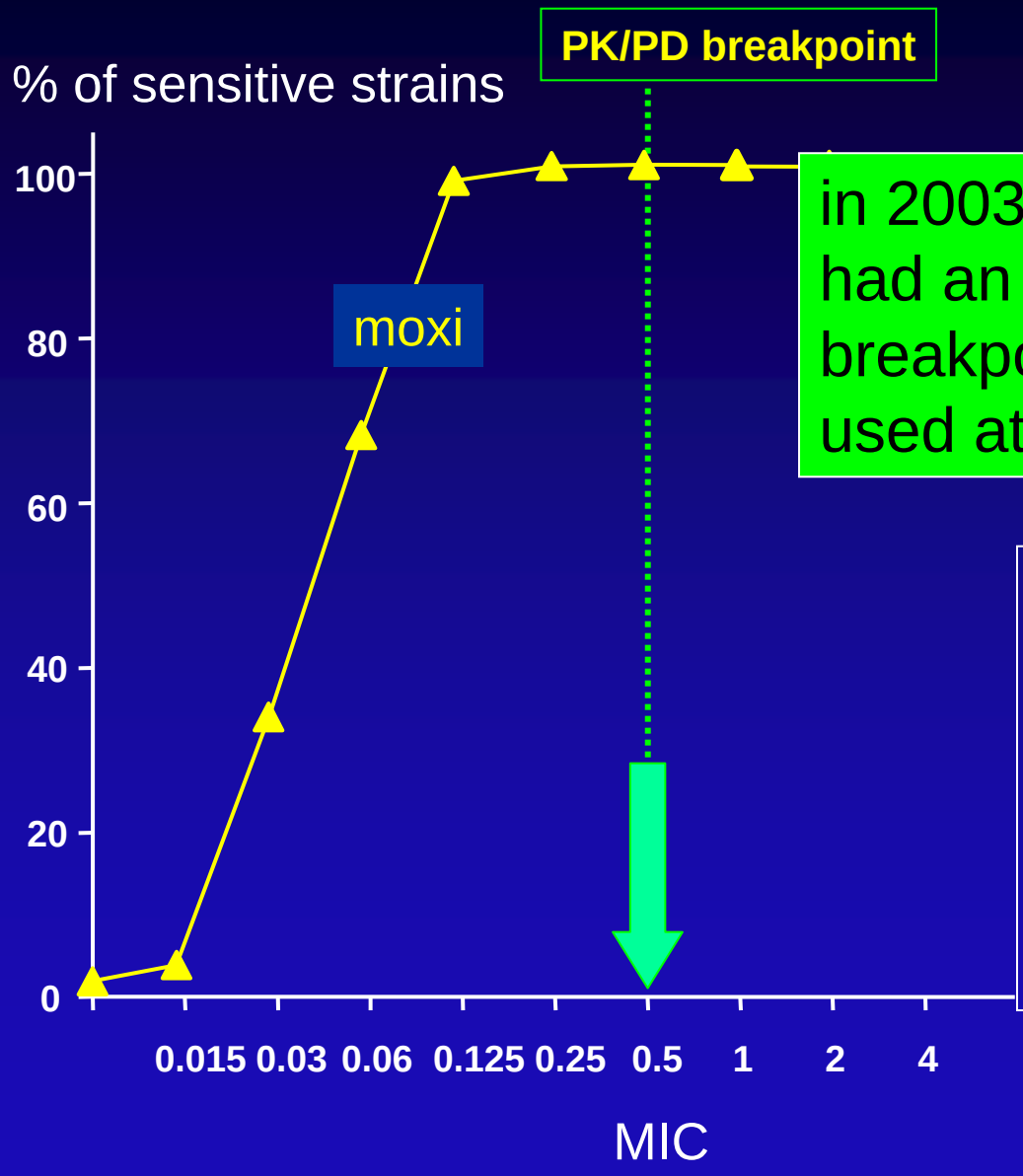


Levofloxacin 500 mg 1X /day

- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- MIC_{max} < 0.5

Should a one-dilution reduction in susceptibility occur as compared to the 2003 values, 95% of the strains would have an MIC higher than the PK/PD ... Except if the dose is doubled ...

Application to pneumococci in Belgium ...



in 2003, all the Belgian strains had an MIC below the PK/PD breakpoint if moxifloxacin is used at a daily dose of 400 mg

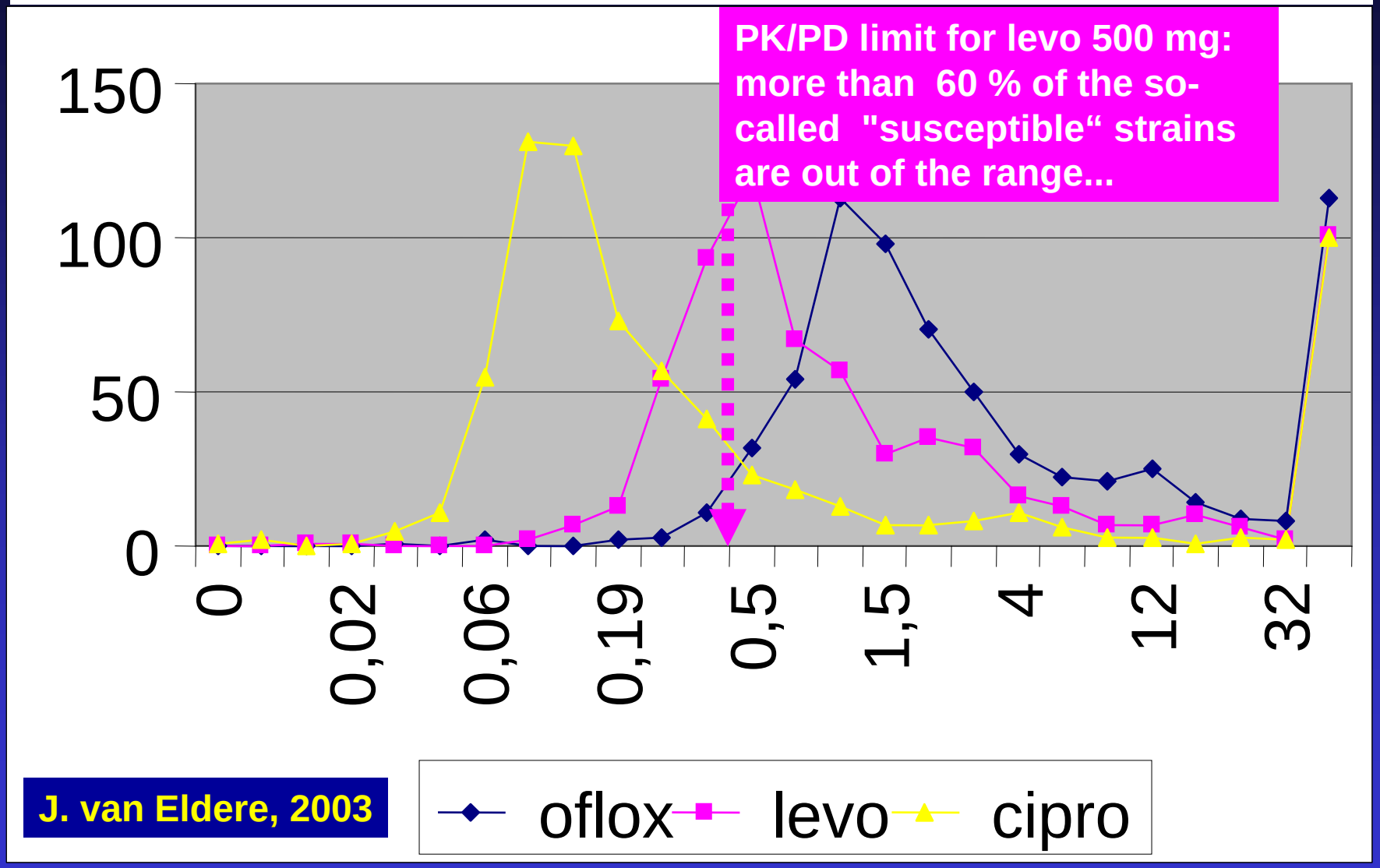
Moxifloxacin 400 mg 1X/day

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
- MIC_{max} < 0.5

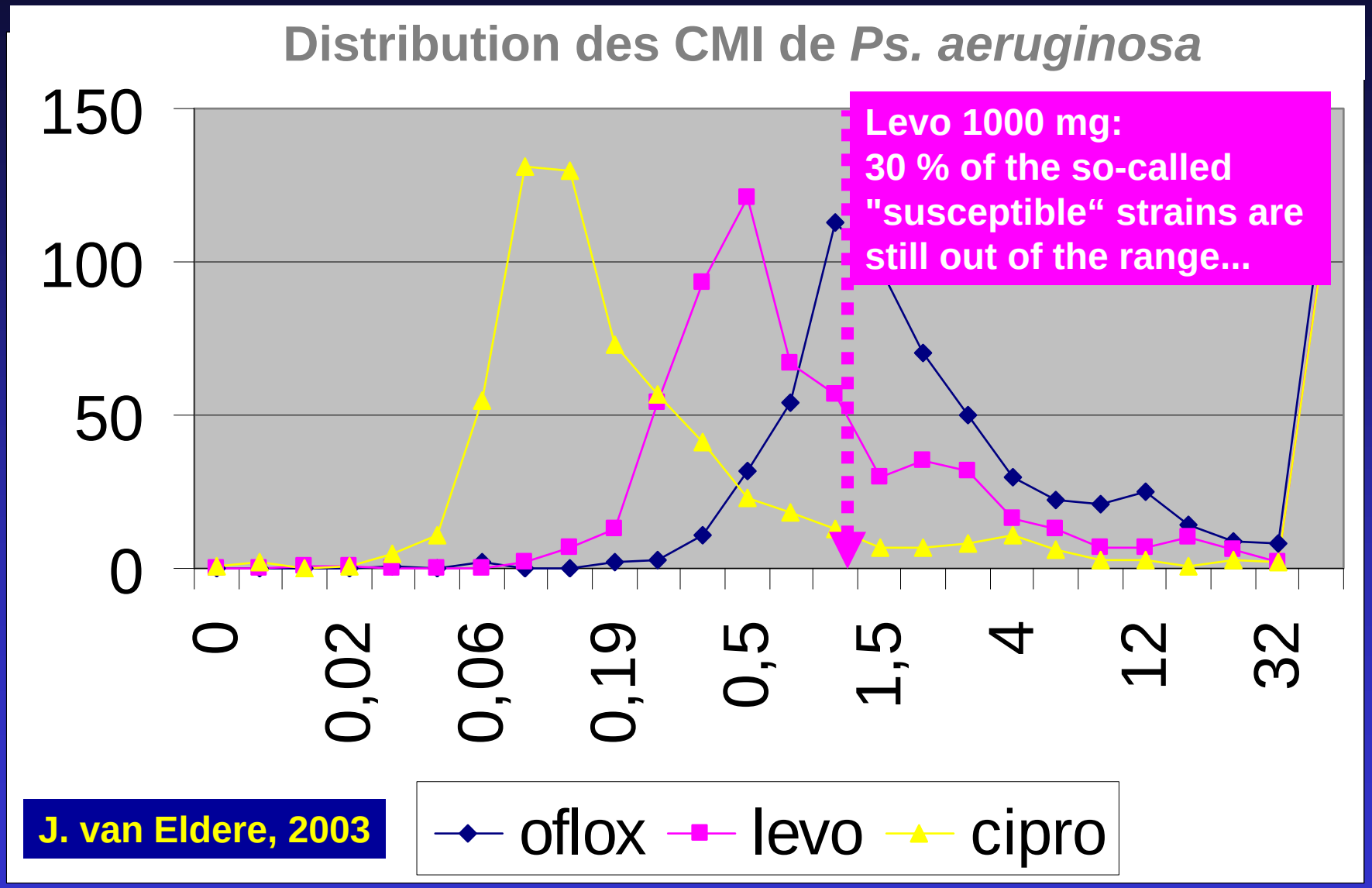
MIC data: J. Verhaegen et al., 2003

Can we do the exercise for *P. aeruginosa ?*

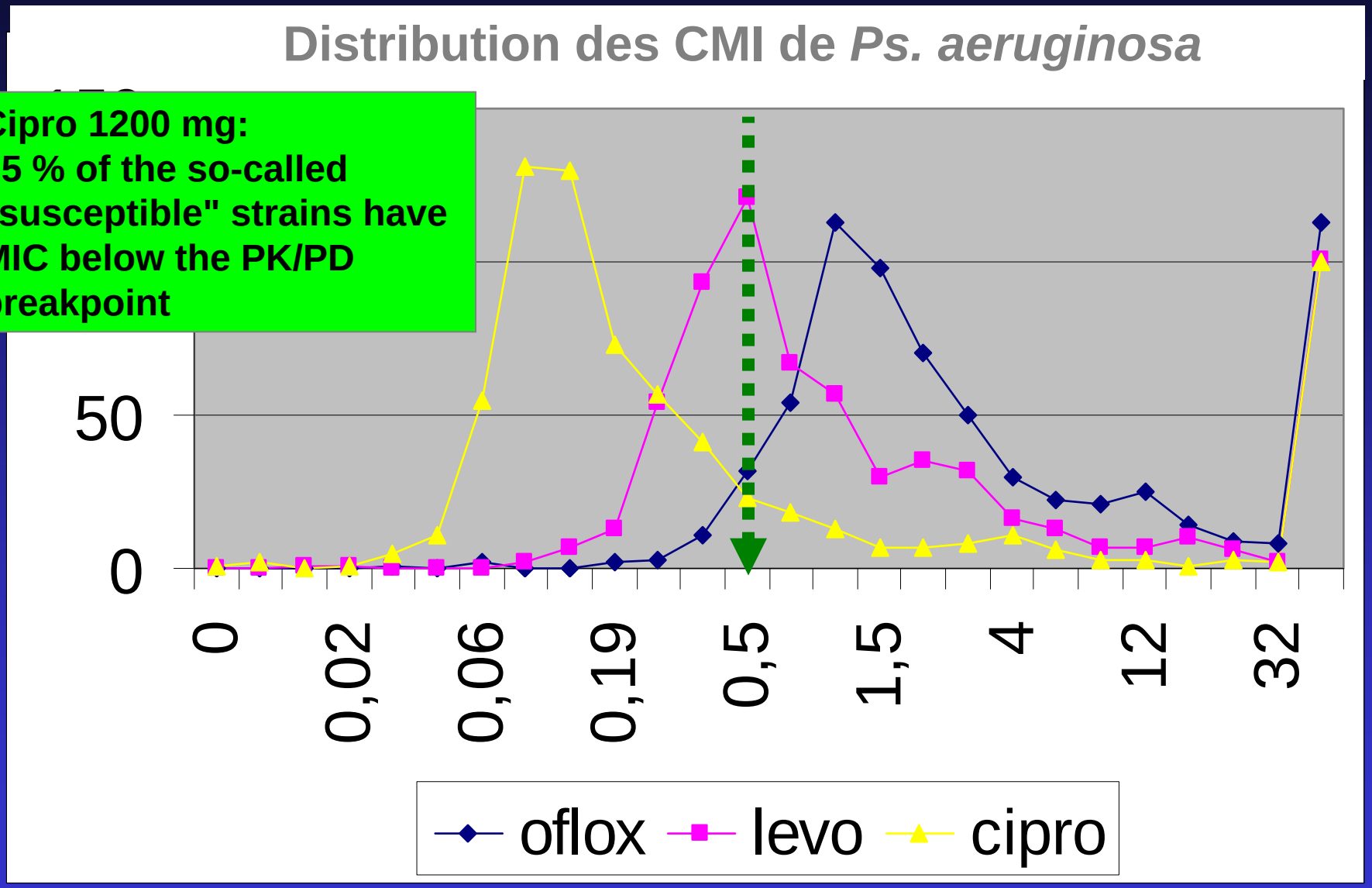
MIC distributions for *P. aeruginosa*



Can we do the exercise in Belgium *?*



Can we do the exercice in Belgium ?



Rational basis of quinolone choice…

- Knowledge of local epidemiology
  - **MIC distributions …**
- Calcuation of the PK profile necessary to obtain an optimal activity on > 90 % of the target organisms
  (in terms of AUC and peak)
  - **consider a safety margin (MPC …)**
- Comparison between proposals …